

# Organoid biobanking: identifying the ethics

*Organoids revive old and raise new ethical challenges for basic research and therapeutic use*

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Recent developments in stem cell research and genomics have made it possible to grow mini-organs, so-called organoids, in culture. Organoids are self-assembling three-dimensional structures that closely resemble the architecture and function of real organs and are seen as one of the most significant developments in stem cell research with a wide range of applications in research and in the clinic. However, the relevant ethics for organoid technology have not been sufficiently addressed. First, the moral and legal status of organoids deserves further exploration. Second, organoid biobanking calls for the development of adequate consent procedures in both research and clinical applications. Third, the concept of mixed models in biobanking of organoids requires distinct governance structures. Fourth, we anticipate ethical challenges related to clinical translation. Further interdisciplinary discussion is required to stimulate morally responsible innovation.

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Organoids can be grown from several types of stem cells, including induced

pluripotent stem cells (iPSCs), human embryonic stem cells (hESCs) and adult stem cells for a wide variety of organs including gut, kidney, pancreas, liver, brain, and retina, among others. These mini-organs can be stored in biobanks and used for fundamental research, precision medicine, and regenerative medicine [1,2]. Cerebral organoids can be used to understand brain development, and mini-guts can serve as a personalized drug-testing tool for cystic fibrosis (CF) [2,3]. Mini-livers could form a complement to current organ transplantation to restore liver function of patients with metabolic liver disease [2].

Stem cell research, and the use of embryonic stem cells in particular, has raised a fierce ethical debate, which mainly revolved around the moral status of embryos [4]. iPSCs provided an alternative to bypass moral concerns about the destruction of embryos, but, as it turned out, they raised other ethical challenges such as consent, ownership, commercialization, intellectual property rights, and safety; the debate on these topics is ever ongoing. The technological convergence of big data, genomics, stem cell technologies, and biobanking, combined with increasing globalization and the growth of biotechnology, makes it particularly challenging to formulate harmonized ethical guidance. As organoid biobanking is growing rapidly, it should be scrutinized whether and to what extent organoids give new twists to the ethical challenges in stem cell research and analogous fields. Here, we identify key ethical challenges related to the donation, storage, and use of organoids.

Similar to stem cells and stem cell lines, the first key question would address the legal and moral status of an organoid: What kind of entity is an organoid, Who owns it, and What can and cannot be done with it? Answers to these questions could draw on the continuing debate about the legal and moral status of the human body and its parts [4,5]. Central to this debate is whether we own our bodily material and whether it may be exchanged as a commodity. This is a complicated question, because human tissue is neither a person nor a thing [5].

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Traditionally, people donating organs or tissues have personal rights in their body parts, such as rights of control and informed consent [5]. It is often argued that these rights should be limited though, so donors should not have property rights in their biological material, nor should they have the right to sell it. This is mainly based on notions of human dignity and on principles of non-commercialization of the human body [4,5]. Other parties, however, can establish a form of property rights in bodily material, namely if they transform it

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into intellectual property (IP) through an innovative step [4,5]. Consequently, a paradoxical situation could arise, in which individuals have no further rights to downstream use once they have donated the tissue, whereas researchers or companies can make profit out of their IP [5]. This, in combination with the increasing density of the IP landscape, requires us to consider how IP can best be constructed to maximize innovation, while protecting the rights and dignity of the donor [4,5]. This question remains a topic of debate in the stem cell field and becomes increasingly important for organoid technology.

*“... emphasis on the consent paradigm alone may not be sufficient moral justification for using human tissue for organoid technology.”*

First, commercial interest in organoid technology is rising rapidly. Organoids are an exciting and cutting-edge tool for drug development and precision medicine and are therefore very attractive for biotech and pharmaceutical companies. Galapagos has already entered a license agreement for the use of organoid technology for preclinical drug research in CF and inflammatory bowel disease. Organome pursues mass production of brain organoids for research. Furthermore, if organoid transplantation enters a clinical stage, off-the-shelf organoids will be needed.

Second, organoids have a genetic and functional link to the donor, and they are complex entities associated with different categories of biological material, such as tissue samples, cell lines, and whole organs. It is important to examine the moral status of organoids, and the ways in which organoids are related or refer to donors, because this can influence the ethical evaluation of the level of commercialization of organoid biobanking.

Waldby & Mitchell [4] show compellingly that the context of donation, the type of tissue, and the subsequent use or transformation highly influence the value that donors may put on their bodily material. Organoids that are grown out of intestinal biopsies of patients with CF, for instance, could have direct individual benefit as

personalized drug-testing tool [3]. If liver organoids are grown out of iPSCs from a healthy donor, this direct clinical relevance is less likely to occur. Furthermore, the tissue and the subsequent use of the organoids may be more or less sensitive [6]. For instance, cerebral organoids could be particularly sensitive, as these models may reveal personalized cognitive features. In terms of applications, commercial use, gene therapy, and clinical transplantation could be more sensitive than basic research. It would require empirical studies to gauge the perspective of donors and their attitude toward commercial use and distribution of organoids.

A second set of ethical challenges relates to whether, and what kind of, consent is required. The use of human tissue for research purposes has so far been justified by either obtaining the donor's consent or de-identification of the sample [7]. The potential harm related to (residual) tissue donation is mainly related to information and privacy. Consent is therefore usually not required if the tissue is de-identified, because these harms are not likely to realize. However, there is a dispute whether de-identification does indeed justify research on human tissue and whether it guarantees privacy [7]. Notwithstanding, complete de-identification is not desirable for organoid technology, because it will greatly decrease the scientific and clinical value. If removing the identity of the donor is not an option, consent is a requirement.

*“The application of organoids in precision medicine will be at the margin of research and care, and new models are needed that enable integration of both.”*

The emergence of biobanking, stem cell banking, and genomics has already challenged more traditional notions of specific consent, in particular as it is impossible to know the scope and direction of future research in advance [7]. Organoid biobanking, as a convergence of these technological developments, encompasses these consent challenges. Whereas a thick opt-out—that raises awareness about the opt-out

procedure, provides adequate information, presents a genuine possibility to object, and adequately registers objections—is often considered sufficient for traditional biobanks with residual tissue [6], this would not suffice for organoid technology, because of the potential sensitive uses. Several solutions for an appropriate opt-in procedure have been proposed, including broad consent, tiered consent, and dynamic consent [6,7].

*“If the ethical challenges are only scrutinized separately, chances are that what may seem a solution to one question, could conflict with other areas.”*

Apart from the need for evaluating the appropriate consent procedure, emphasis on the consent paradigm alone may not be sufficient moral justification for using human tissue for organoid technology. Is consent able to fulfill all moral requirements brought forward by the characteristics of organoid technology, or will it become, as some called it in analogous fields, an over-stretched and eroded concept [5]? It is therefore worthwhile to explore what could justify the storage, distribution, and use of organoids in addition to the requirement of consent.

The storage of organoids will serve the combined goals of future research and clinical purposes. This mixed model of biobanking brings along a distinct set of ethical challenges. First, the traditional research infrastructure of biobanking may be unsuitable when organoid technology moves toward the clinic. Biobank storage for research purposes has the main goal of generating scientific knowledge, whereas for a clinical biobank, the interests of patients take precedence. This requires distinct ethical oversight. Moreover, if organoid technology is implemented in precision medicine, a suitable infrastructure is needed with the capacity for clinical validation of results and for responsibly returning results to patients. In addition, data storage and linkage should be tailored to the clinical needs of patients, while safeguarding their privacy. Furthermore, if organoids are used for clinical transplantation, it requires off-the-shelf organoids

of clinical-grade quality, which have to comply with good manufacturing practices (cGMPs) in order to ensure safe clinical use.

Second, the clinical relevance of organoid technology further accentuates the discussion on public or private models of biobanks [4]. Organoids could be distributed globally, and research on organoids may lead to a complex patenting landscape, similar to that of iPSCs. Both public and private stakeholders may well be interested in organoid technology, which urges us to examine which proportion between both parties is ethically desirable. Whereas the establishment of public-private biobanking models may accelerate translational research for the eventual benefit of patients, it also requires considerations of benefit, data sharing, and the maintenance of trust.

A fourth set of ethical challenges concerns the clinical use of organoids. A first point relates to precision medicine and translating the response of organoids in the laboratory to drugs toward the clinical needs of a patient. Although the organoid model closely mimics the dysfunction of the original organ, it does not account for an entire body, or for the broader context of the patient. It could therefore be challenging to clinically validate the *in vitro* response to drugs, especially in patients with rare diseases [3].

The application of organoids in precision medicine will be at the margin of research and care, and new models are needed that enable integration of both. One avenue worthwhile to explore could be the implementation of “n-of-1” trials: single-patient randomized controlled trials with multiple crossovers [8]. Nonetheless, such a design may bring along ethical challenges such as the appropriate framework of ethical review, cost-effectiveness, data sharing, and consent.

A second ethical point regards the reimbursement of drugs. Although reimbursement policies vary per country, personalized drug testing in organoids may challenge prevailing practices, which depend on evidence of safety and efficacy from large-scale clinical trials. Testing drugs in organoids generates data on effectiveness in individual patients or in smaller groups, which is a novel type of evidence.

An example of this potential conflict in reimbursement policies is the use of organoids within precision medicine to treat

**Sidebar A: Further reading**

**Organoid technology**  
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 Chakradhar S (2016) New company aims to broaden researchers' access to organoids. *Nat Med* **22**: 338

**Clinical translation**  
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 Habets MG, van Delden JJM, and Bredenoord AL (2014) The inherent ethical challenge of first-in-human pluripotent stem cell trials. *Regen Med* **9**: 1–3

**Biobank governance**  
 O'Doherty KC, Burgess MM, Edwards K, Gallagher RP, Hawkins AK, Kaye J, McGaffrey V, and Winickhoff DE (2011) From consent to institutions: Designing adaptive governance for genomic biobanks. *Soc Sci Med* **73**: 367–374

patients with CF. This is a life-shortening hereditary disease in which thick and sticky secretions from various glands lead to gastro-intestinal and pulmonary complications. It is caused by ~2,000 mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, and the large majority of mutations are rare [3]. For decades, treatment has been mainly symptomatic, but drugs that target mutation-specific defects of the CFTR protein are now being developed. Kalydeco, which costs around US\$275,000 per patient per year, has been approved for a select subset of CF patients (~5–6%) that express so-called gating mutations [3, <http://www.ema.europa.eu/ema/>].

In the Netherlands, Kalydeco has been tested using a functional CFTR assay on gut organoids of CF patients whose mutations fall outside of this approved scope [3]. If the

treatment is effective, improved CFTR function causes ion and fluid transport into the organoid lumen that can be quantitated by measuring organoid swelling, which is completely CFTR dependent [3]. Although a subset of patients turned out to be drug responders, they were not eligible for reimbursement. After negotiations among physicians, scientists, the government, and the National Health Care Institute, three subjects now receive treatment and are reimbursed. Further discussion about reimbursement of drugs based on organoid data is ongoing. Similar challenges may occur in other applications, such as targeted therapy in oncology. Therefore, proactive scrutiny and potential adaptation of current practices are needed.

Another important promising application of organoids is transplantation, for example,

in treating liver disease. Although experiments are currently in a preclinical stage, the first clinical use in humans should be anticipated. At least three types of ethical challenges have been identified when setting up complex translational trials, which are “first-in-human trials involving several invasive interventional and study procedures” [9]. First, early human studies are ethically challenging because the required evidence to predict risk and benefit in humans is lacking. The assessment of risks and uncertainties is especially vital in complex translational trials [9]. A first-in-human (FIH) organoid trial will require extensive attention to reduce risks and uncertainties, to maximize the scientific and social value and to assess whether making the leap from bench to bedside is justified. Second, choosing the most appropriate study population—that is both ethically suitable and sufficient to answer the research question—is challenging, even more so when first use would be a pediatric trial for children with inherited metabolic disease. Third, there are questions concerning the right study design with the right choice of outcomes and comparators. Traditionally, a FIH trial is a safety study, but there are debates whether outcome measures should not also take efficacy into account in order to maximize benefit.

**O**rganoid biobanking is a promising and exciting new field with considerable potential for scientific research, precision medicine, and regenerative medicine. We identified four interrelated ethical challenges for research and clinical use. Although these are not new, organoid biobanking is a complex technology in which several ethical discussions converge. The moral evaluation of this rapidly growing field requires an integration of these diverse topics, rather than an isolated assessment of

either challenge. If the ethical challenges are only scrutinized separately, chances are that what may seem a solution to one question could conflict with other areas. An essential question is therefore how we can integrate the different domains.

It is vital to involve all the different stakeholders in the debate on the development of adaptive governance structures. This includes the active and substantial participation of donors. A first step would be to investigate the perspectives, opinions, and attitudes of patients and (potential) donors toward organoid technology. In addition, it is important to develop novel notions of benefit sharing [10], especially in light of the increasing commercialization and globalization of organoid biobanking. The idea of benefit sharing is twofold. It encompasses specific benefits to individual participants or to participant groups, such as feedback of results or access to treatments, for their efforts and contribution and embraces the generation of benefit for society at large [10]. After all, the rationale of the public good, or social value, is frequently put forward as a moral justification for the use and exchange of human tissue. This rationale should not be taken for granted within organoid biobanking. It calls for further reflection, particularly because organoid technology crosses several boundaries between seemingly opposing categories, such as the public versus the private, and clinical versus research. Responsible advancement and implementation of organoid biobanking requires an optimization of its potential for clinical, scientific, and social values, while respecting and fostering the rights and interests of participants.

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### Conflict of interest

The authors declare that they have no conflict of interest.

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